EXPERT REVIEWS

Managing corneal ectasia prior to keratoplasty

Expert Rev. Ophthalmol. 10(1), 33–48 (2015)

Fernando Faria-Correia[1–6], Allan Luz[6–8] and Renato Ambrósio Jr*[6,8–10]

[1]*Cornea and Refractive Surgery Department, Hospital de Braga, Braga, Portugal*
[2]*Instituto CUF, Porto, Portugal*
[3]*Oftalconde, Porto, Portugal*
[4]*Clínica Oftalmológica Dr Horácio Correia, Bragança, Portugal*
[5]*School of Health Sciences, University of Minho, Braga, Portugal*
[6]*Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, Brazil*
[7]*Hospital de Olhos de Sergipe, Sergipe, Brazil*
[8]*Universidade Federal de São Paulo, São Paulo, Brazil*
[9]*Cornea and Refractive Surgery Department, Instituto de Olhos Renato Ambrósio, Rio de Janeiro, Brazil*
[10]*VisareRio, Rio de Janeiro, Brazil*
*Author for correspondence:
renatoambrosiojr@terra.com.br

The advent of refractive surgery allowed for great advances in the understanding of pathophysiology, diagnosis and treatment of corneal ectatic diseases. The different associations that highlight the importance of this range from the need for early diagnosis in the screening process of candidates for laser vision correction to the impact of refractive surgery technologies on treatment. Keratoconus is still an indication for corneal transplant, and it is expected that about 5–20% of the patients may require it. However, considering technological advances, the current treatment options are diverse and can be customized to each case. This review overviews the fundamental knowledge related to corneal ectatic diseases management and its management prior to keratoplasty. Whereas this is an area of dynamic development of scientific knowledge, we present fundamental concepts, along with information on the most recent studies and future prospects.

KEYWORDS: corneal biomechanics • corneal ectasia • corneal tomography • crosslinking • enhanced screening • intracorneal ring segments • keratoconus • keratoplasty • post-LASIK ectasia • topoguided-PRK

Keratoconus and ectatic corneal diseases have been widely studied for over 150 years [1,2]. However, the advent of refractive surgery has enabled the greatest advances in the understanding of pathophysiology, diagnosis and treatment of such diseases. Understanding ectatic diseases of the cornea is essential for the refractive surgeon. The different associations that highlight this importance varies from the need of early diagnosis in the screening process of selecting candidates for laser vision correction (LVC) to the impact of new technologies related to refractive surgery in the treatment of these diseases [3,4].

Corneal photoablative procedures may induce or accelerate the progression of ectasia [5,6]. Moreover, customized surface ablation may be successfully performed in case of keratoconus, with both refractive and therapeutic purposes [7]. However, the indication for elective refractive procedure should be well thought out and conscious.

Knowledge about the structural, geometric and optical properties of the cornea is crucial. Advances in corneal evaluation tools are essential to identify candidates for LVC with higher risk (or susceptibility) to ectatic progression. Such information is equally important to indicate and schedule the surgery. Thus, additional workup should be done using technology with the ability to generate such data, which must be properly interpreted by the surgeon [4,8–11].

Corneal ectatic diseases

Corneal ectasia is a condition characterized by biomechanical failure [12]. The cornea is under constant stress as a result of the intraocular pressure, as well as stress generated by the eyelids, the extraocular muscles or other external trauma sources. Eye rubbing has a great impact in corneal 'biomechanical stress' [13]. There is a 'structural susceptibility' that is related to individual genetics and is the determinant of the biomechanical properties of the cornea.

Biomechanical failure leads to thinning and tissue protrusion without an acute inflammatory process. Recent studies indicate that chronic inflammatory activity may be involved in the pathophysiology of these diseases. The changes are progressive and cause astigmatism and irregularities (high-order aberrations), which may or may not be associated with myopia [12].

Keratoconus is the most common ectatic disorder, and its incidence is classically described as one patient per 2000 inhabitants [1,2,14]. However, some studies indicate a higher incidence of the disease. For example, such a condition is identified in about 1–5% of candidates for refractive surgery, which is certainly related to a process of self-selection,

10.1586/17469899.2015.991390

ISSN 1746-9899

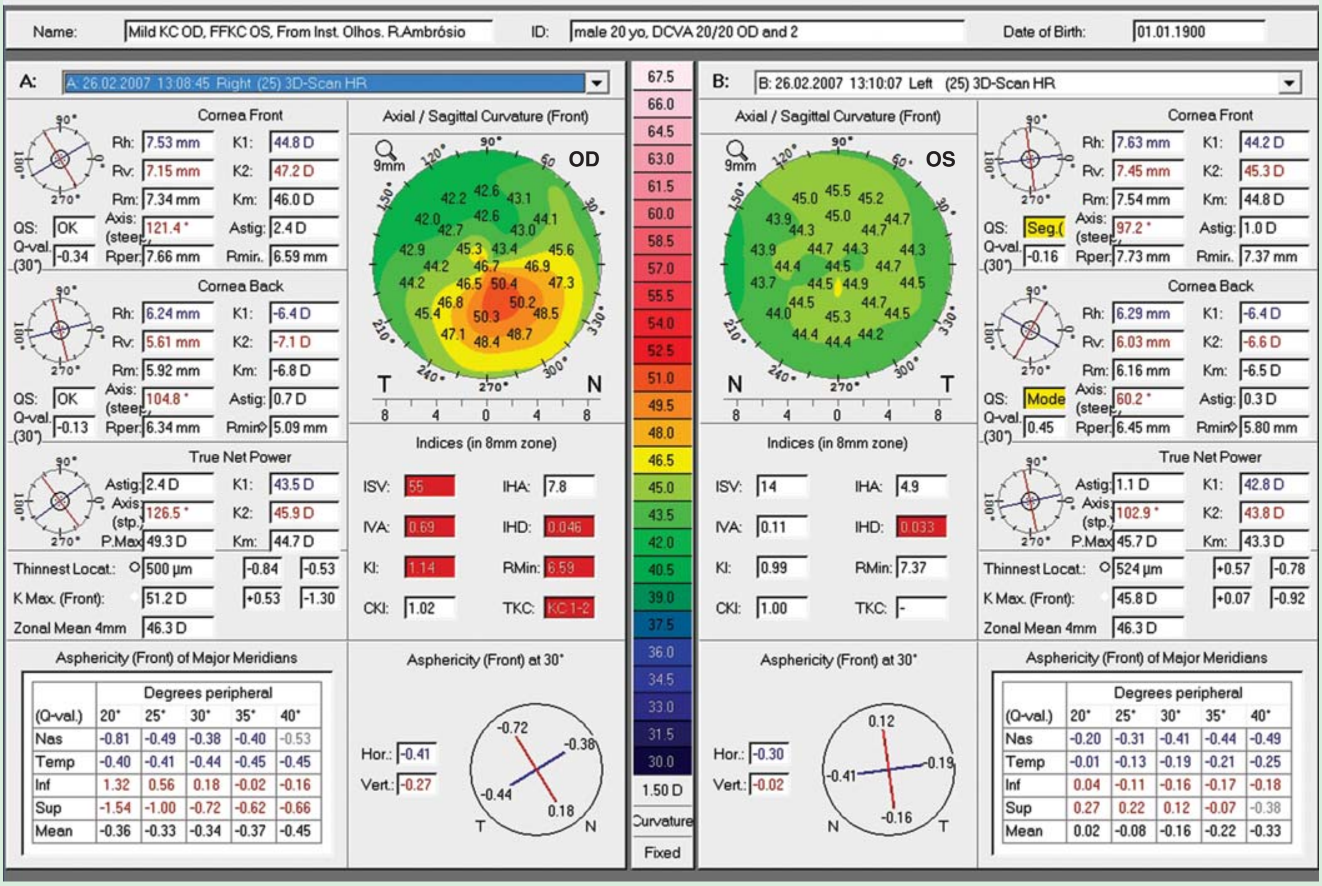

Figure 1. Anterior curvature sagittal map of a patient with mild keratoconus OD and forme fruste keratoconus OS.
OD: Right eye; OS: Left eye.

as each patient with keratoconus is more likely to seek help because of their visual impairments [3,10]. It is a progressive and bilateral disease, but can be quite asymmetric. It may be associated with systemic diseases such as Down syndrome, retinitis pigmentosa, Leber congenital amaurosis, mitral valve prolapse and other connective tissue diseases, such as Ehlers–Danlos and Marfan syndrome. However, one of the most important associations is related to ocular allergic diseases, such as atopic dermatitis and vernal keratoconjunctivitis [1,2,14].

Besides keratoconus, other disorders that are classified within this group of natural ectatic diseases are pellucid marginal degeneration (PMD) and keratoglobus. Such conditions are rarer than keratoconus and are identified based on the pattern of thinning [1,2]. PMD has a thinning ‘band’ in the inferior cornea near the limbus, which induces flattening of the vertical meridian and astigmatism against-the-rule [1,15]. The topographical feature (anterior curvature) in some cases with inferior keratoconus may be similar to the PMD, but differentiation is possible by means of a pachymetry map [1,2]. The term ‘pellucid’ means transparent, being an avascular condition and free of acute inflammation and lipid deposits, which differentiates PMD from other diseases, such as Terrien’s marginal degeneration and Mooren’s ulcer, which are not considered as ectatic diseases [1,2]. Keratoglobus is a condition even more rare that PMD, defined by overall thinning of the cornea and severe protrusion, with a significant increase of the anterior chamber depth [1]. Therefore, the differentiation between keratoconus, PMD and keratoglobus is possible only through the pattern of thinning [2,16]. Proper classification has clinical relevance, since clinical aspects and therapeutic management are distinct. Ectasia progression with thinning and tissue protrusion may also occur after trauma or surgical procedures. Such situations can lead to biomechanical failure of corneal stroma and consequent ectasia. It is vital to recognize that ectasia can occur after refractive corneal surgery performed through different techniques such as radial keratotomy, laser-assisted *in situ* keratomileusis (LASIK) and photorefractive keratectomy (PRK) [5,6,17–19]. The appropriate selection of candidates for refractive surgery is the key to prevent this severe complication, with the essential understanding and interpretation of ancillary tests [4,8,10].

Clinical evaluation of ectatic corneal diseases

Early diagnosis of keratoconus is fundamental as it may enable the early application of therapeutic strategies that minimize the effect of the disease on the patient and society. Keratoconus is generally diagnosed or suspected during general ophthalmological examination, but ancillary exams play a major role in the diagnosis, staging and follow-up of the condition [1]. For example, Marc Amsler published for the first time the 'forme fruste keratoconus' concept, based on photokeratoscopy imaging, in a prospective study [20]. The detection of early forms of ectatic disease is also essential in the screening process of candidates for LVC, in order to prevent progressive iatrogenic ectasia [3,8,10].

In the mid-1980s, Stephen D. Klyce, PhD, first developed algorithms for surface reconstruction of the acquired reflection image from Placido-based videokeratoscopy, allowing color-coded maps and quantitative data of the front surface of the cornea [21]. Corneal topography represented a true revolution in the diagnosis and management of corneal disease [22]. It requires caution about the scan quality, because artifacts may affect the clinical presentation [4]. Regarding ectasia, the topographic pattern of inferior steepening is the most recognized one [3,23]. However, there is a great variation in the subjective classification of topographic maps, being required to define objective criteria [9]. In general, higher corneal values to 47.5 D are suspected. Additionally, the asymmetry between the values in the 3 mm radius in the upper and lower regions (or between the nasal and temporal regions) is suspected when greater than 1.4 D [24,25]. Such parameters are integrated in the calculation of the keratoconus percentage index, described by Rabinowitz and Rasheed [26]. In addition, several indices derived from curvature data are available in different commercial devices.

Other technologies were a further improvement in corneal imaging, such as corneal tomography (CTm) [27]. This technology provides a 3D image of the cornea and may be possible through different methods, such as rotational scanning Scheimpflug, optical coherence tomography and a very-high-frequency ultrasound [27]. The tomographic approach characterizes the anterior and posterior surfaces of the cornea, allowing elevation and thickness maps. The evaluation of the pachymetric distribution allows an understanding of the structural stability of the cornea [28]. Since there is an increase in thickness from the center to the periphery, this gradual thickening ratio has a normal range. Ectasia causes changes in this pattern of pachymetric spatial distribution, with a steeper increase of the thinned area toward the periphery [28,29]. The study of the epithelium thickness, which was only possible with very-high-frequency ultrasound previously, is now available with spectral- or Fourier-domain optical coherence tomography [30,31]. The epithelium reacts to stromal changes, so the knowledge of its thickness and pattern are very important for the evaluation [30,32]. Studies that consider elevation and pachymetric distribution data show that CT is more sensitive in identifying mild forms (forme fruste or subclinical)

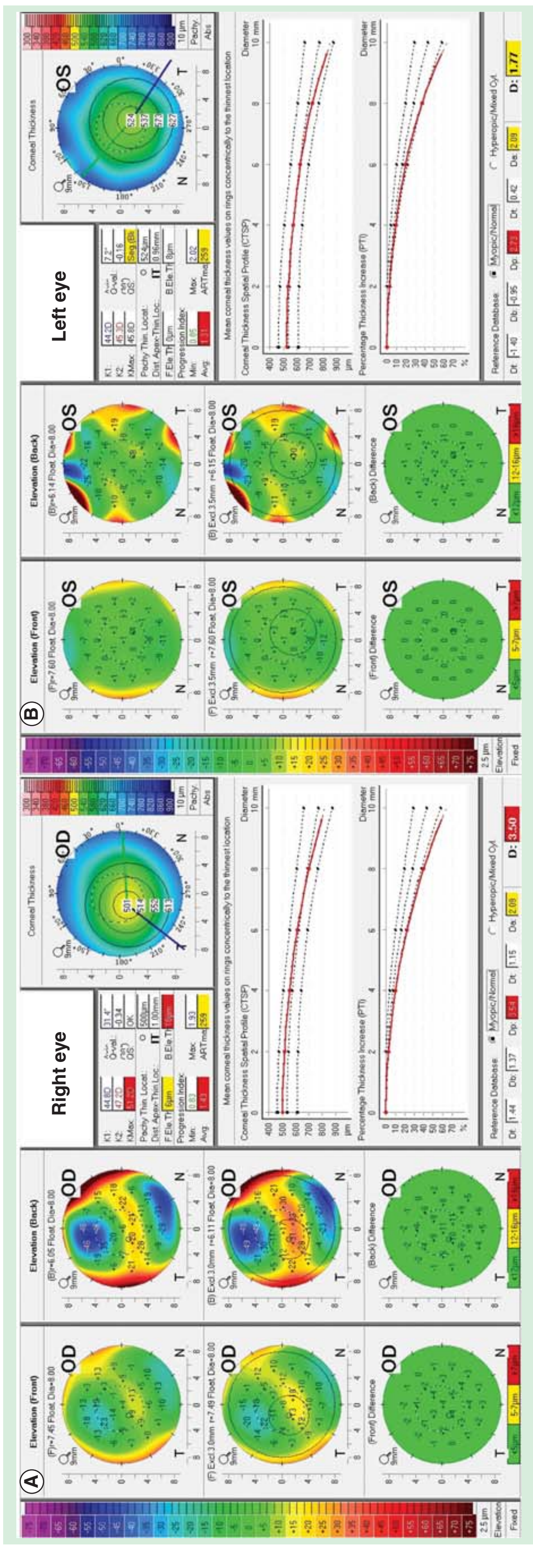

Figure 2. Belin/Ambrósio enhanced ectasia display showing abnormal values for posterior elevation and thickness distribution. (A) OD with mild keratoconus and **(B)** OS with forme fruste keratoconus.
OD: Right eye; OS: Left eye.

Table 1. Surgery indications in cases with ectatic diseases.

Aim	Clinical background/history
Visual improvement	Patient with poor vision corrected by glasses and/or contact lenses
Stabilize the evolution of ectasia	Documented progression of ectasia or evidence of high risk for vision loss

of the disease compared to the anterior curvature topography [28,29,33]. Illustrative examples are patients with keratoconus diagnosed in one eye and with normal topography in the contralateral eye (Example 1). Such cases are considered as asymmetric keratoconus [4,6,10].

Example 1: Male, 20 years old, with asymmetric keratoconus presented with best-corrected visual acuity (BCVA) in both eyes (20/20 right eye [OD] and 20/15 left eye [OS]). The relatively normal topography pattern is identified in the left eye, while mild keratoconus in observed in the right eye (Figure 1). The combination of tomographic elevation and thickness data enhances the ability to detect ectatic disease, as proposed in the Pentacam Belin/Ambrósio Enhanced Ectasia Display [16,34]. The Ambrósio relational thickness – maximum [29] was 259 in both eyes (Figure 2). The final final deviation value was 3.50 and 1.77 in OD and OS respectively, which is consistent with the clinical diagnosis. This example represents a very mild (forme fruste) keratoconus in the left eye, which has still relatively normal curvature topography but has moderate changes on tomography [4,6,10,35].

Regarding refractive surgery screening, classic methodology includes Placido-disk-based corneal topography and central corneal thickness measured by ultrasound [3,4,25]. The ectasia risk score system, which takes into account the topographic classification, proved to be an improvement for the refractive surgery screening process [36,37]. Some studies have shown the drawbacks of this scoring system, revealing high rates of false positives and negatives [6,10,38–40]. There are well-defined risks for ectasia after LVC, and these may be related to the presence of ectasia (typically mild) preoperatively, or a procedure that determined important changes in corneal biomechanics [10]. Considering these concepts, any cornea may evolve into ectasia if surgery or trauma weakens its biomechanical structure. This can occur in LASIK due to a thick flap or excess tissue ablation, or even after a blunt trauma. The likelihood of developing ectasia combines the structural susceptibility of the cornea with the impact of surgery [4,10]. Therefore, the process of screening the risk for developing ectasia must go beyond the detection of mild forms of keratoconus or related diseases [4,8,34]. It is necessary to evaluate the biomechanical properties of each cornea to access the susceptibility of failure and ectasia progression, which would be a feature inherent in any cornea. Retrospective studies of preoperative examinations of patients who developed ectasia also confirm that the tomographic approach is superior to topography [6,10,40]. Furthermore, CT does not replace the topography, which has advantages, including the qualitative assessment of the tear film [3,41]. The combination of curvature, anterior and posterior elevation and pachymetry data is the most efficient approach for the identification of mild forms of ectasia [4,6,8,10].

While accomplishing new studies to combine tomographic parameters in order to increase the accuracy for diagnosing corneal ectasia and its susceptibility [10,11,42], we need to characterize the cornea beyond its geometry [12,43]. The biomechanical analysis can be performed with dynamic systems of non-contact tonometry, which monitor the deformation of the cornea by means of infrared reflection (Ocular Response Analyzer; Reichert Inc., Depew, NY, USA) or by Scheimpflug imaging (Corvis ST; Oculus Optikgerate GmbH, Wetzlar, Germany) [4,44–48]. Besides these advancements, genetic evaluation by molecular biology is promising in order to help to identify cases with predisposition to ectatic disorders [49].

Ocular wavefront analysis is important to assess the visual quality, as well as to plan the visual rehabilitation of corneal ectasia cases [50]. Other tests that may be relevant are confocal and specular microscopy and ocular biometry [51,52]. Evaluation with endothelial cell count is important, since such patients are typically users or candidates for contact lenses. Confocal microscopy may be useful, as it has been demonstrated that the anterior and posterior stromal keratocyte densities were statistically lower and stromal nerve diameter was statistically higher in patients with keratoconus compared with controls [53]. Biometry allows characterizing nearsightedness (keratometric vs axial), being relevant when planning surgery. Additionally, potential acuity meter and retinal mapping are relevant for determining the prognosis of visual improvement after the correction of optical aberrations and to study the periphery of the retina in eyes typically larger in axial length.

Table 2. Surgical alternatives to corneal transplantation for ectasia.

Procedure	Aim
Intracorneal ring segment	Regularization of corneal surface (‘tissue add’) reduction of irregular astigmatism
Crosslinking	Stabilization or avoid progression of the disease
Advanced surface ablation or phototherapeutic keratectomy	Regularization of corneal surface (‘tissue removal’) reduction of irregular astigmatism
Conductive keratoplasty	Regularization of corneal surface (‘tissue remodeling’) reduction of irregular astigmatism
Phakic intraocular lens	Treatment of spherical or sphere–cylindrical refractive errors (regular astigmatism)
Cataract or refractive lens extraction	Cataract removal, along with treatment of spherical or sphere-cylindrical refractive errors (regular astigmatism)

Elective or therapeutic approach

The differences between therapeutic and elective approaches must be recognized and taken into account, since the same surgical procedure can present both aims [54]. An elective refractive surgery procedure is an effective alternative to other forms of vision correction, such as glasses or contact lenses, which can provide a satisfactory solution. However, the decision to undergo such procedures should be taken exclusively by the patient, based on knowledge about the risks, benefits and limitations of such procedures [55].

To differentiate refractive surgery for therapeutic purposes, we need to focus on the preoperative background. In this situation, the correction by means of glasses or contact lenses is relatively inadequate and unsatisfactory for the patient. This can occur at varying levels of limitation of visual acuity (quantity) and quality. For example, the visual acuity may be less than 20/400 in a case of advanced keratoconus or even 20/20 in a case of irregular astigmatism that causes severe impairment of visual quality. In these cases, elevated magnitudes of higher order aberrations are typically present and keratoplasty may be considered. Ultimately, the therapeutic refractive procedure is presented as a less invasive alternative to keratoplasty for visual rehabilitation [55].

In therapeutic surgery, the main goal is to enable vision correction by sphere–cylindrical refraction (glasses) or even facilitate contact lens fitting. Thus, the measure of success will be related to the improvement in BCVA, with refractive result being the secondary goal. In refractive surgery, the goal is refractive error reduction to provide uncorrected vision and greater independence from glasses or contact lenses. With this, the uncorrected visual acuity is the main variable that represents the effectiveness of the refractive procedure. However, comparison of the pre- and postoperative corrected visual acuity is always related to the safety of any ophthalmic surgery [55].

With the evolution of the initial therapeutic treatment, a case may be purposed for a secondary procedure with a refractive aim [55]. For example, secondary implantation of a phakic intraocular lens has a refractive goal in a patient with BCVA improvement after implantation of intracorneal ring segment (ICRS). The combination of surgical procedures with different purposes is the basis of the 'Therapeutic Bioptics' concept [56]. The informed consent process should be performed with appropriate explanation to the patient, who must understand the differences between need and possibility, weighing up the risks, benefits and limitations of the procedure.

Several therapeutic procedures were originally described with a refractive purpose. The implantation of intrastromal corneal ring for keratoconus is the best example. While its initial refractive indication for myopia and astigmatism was greatly reduced, mainly because there were other more efficient alternatives, this

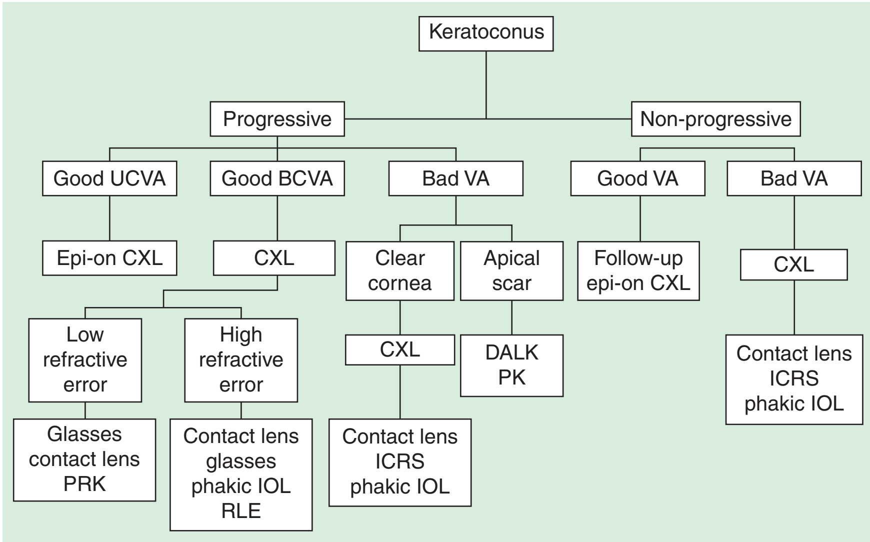

Figure 3. Decision tree for keratoconus surgical management.

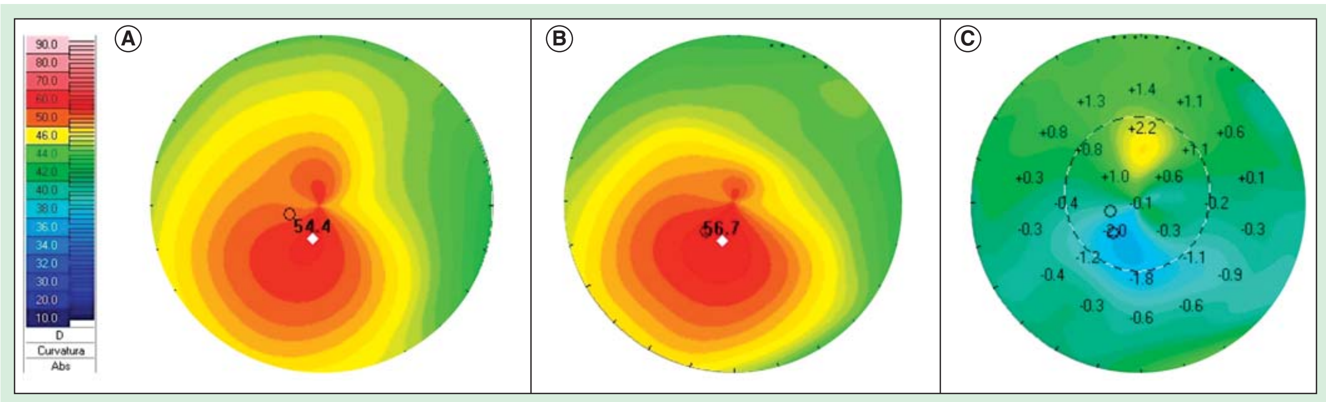

Figure 4. Differential axial curvature map showing flattening and reduction of the corneal irregularity. (A) 8 months after transepithelial crosslinking; **(B)** preoperative and **(C)** differential.

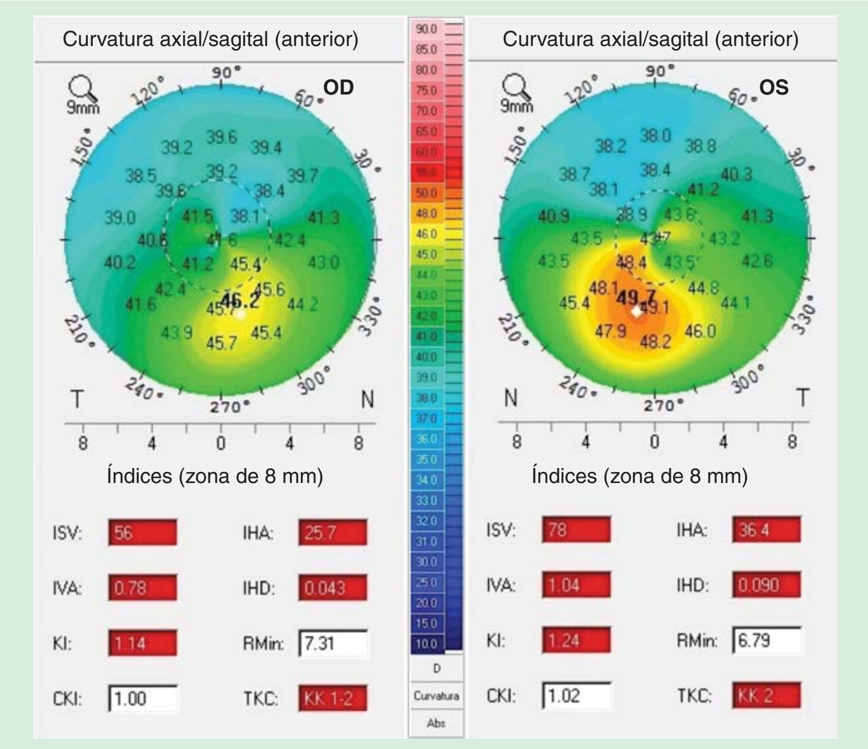

Figure 5. Preoperative axial curvature map of a patient with asymmetric keratoconus and anisometropia in OS. Visual acuity was 20/20 (+0.50 = –1.50 × 90°) in OD and 20/30 (+0.25 = –4.00 × 108°) in OS.
OD: Right eye; OS: Left eye.

modality has proven to be beneficial for patients with ectatic corneal diseases [57,58].

There are procedures that can be performed in a similar way and with therapeutic and refractive goals. For example, a patient with anterior stromal scarring associated with irregular astigmatism, induced by dystrophy or scarring after keratitis, may benefit from therapeutic surface ablation. In this case, besides the application of excimer laser in phototherapeutic keratectomy mode, the customized ablation in PRK mode is used in a similar way compared to an advanced surface ablation for elective treatment of ametropia. However, the goals of advanced surface ablation in both situations are very different, as well as the postoperative outcome analysis [55,59].

General management of ectatic diseases

The diagnosis of keratoconus has a major impact on the patients and their families, because it is classically recognized as one of the most common causes of corneal transplantation [60]. Thus, the education of the patients and their families about

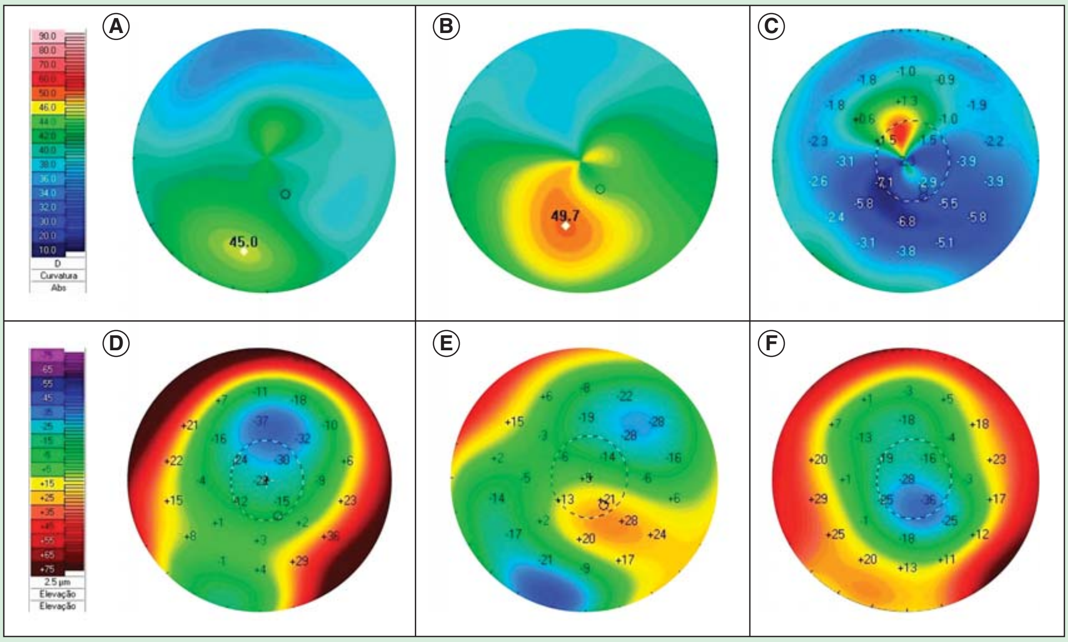

Figure 6. Differential axial curvature (upper row) andanterior elevation (lower row) maps showing flattening and reduction of the corneal irregularity. (A) and **(D)** 12 month after Athens Protocol; **(B)** and **(E)** preoperative; **(C)** and **(F)** differential (same reference sphere used in the elevation maps).

the disease is of fundamental consideration. There are a number of details that patients deserve to know in order to better coexist with the disease. For example, there was a great reduction in the number of corneal transplants for keratoconus due to advances in the diagnostic and therapeutic fields [56].

For visual rehabilitation, glasses represent the first line of treatment. The wavefront-assisted manifest refraction provides a better visual acuity in about 60% of cases [61]. The use of contact lenses is an alternative that provides optical correction. The selection of the contact lens type depends on the stage of keratoconus [62]. The soft lenses with toric design may be adequate for early stages, in order to correct myopia and regular astigmatism. In more advanced cases, rigid gas permeable or hybrid lenses are preferred. These types of lenses can also correct the irregular astigmatism, improving visual quality. However, there is no evidence to support the fact that use of contact lenses reduces the chances of ectatic progression. It has been shown that, similar to the habit of eye rubbing, poorly fitted contact lenses can be associated with disease progression.

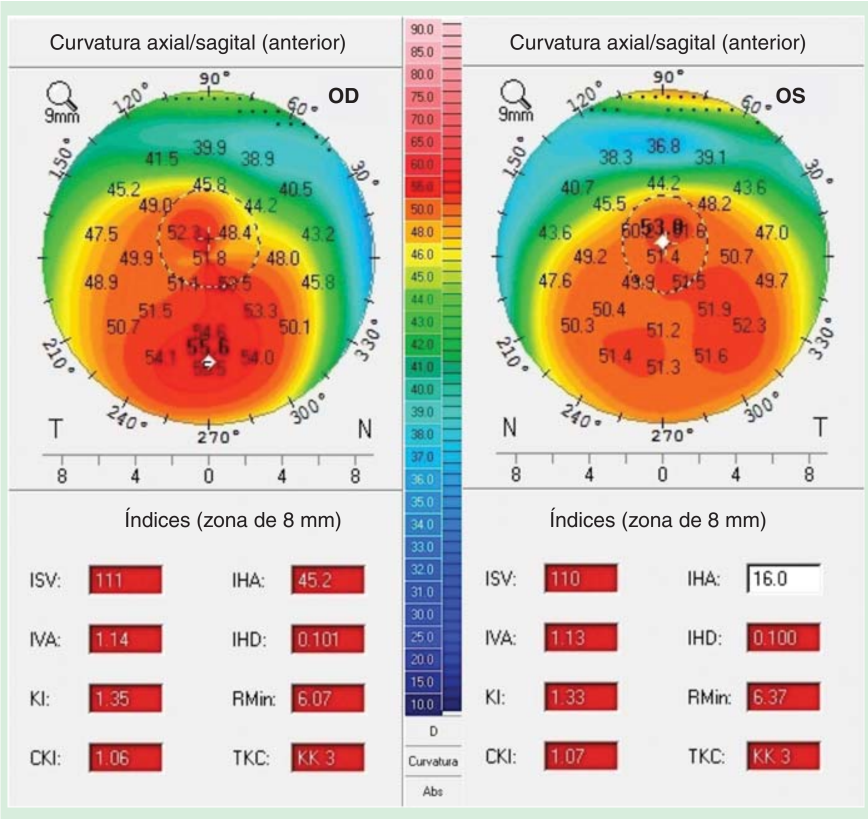

Figure 7. Preoperative axial curvature map of a patient with stage III (Amsler–Krumeich) keratoconus in both eyes.

Keratoconus is a progressive condition and requires monitoring. As mentioned previously, eye rubbing is directly related to its progression [13]. Thereby, allergy control with anti-histamines, mast cell inhibitors along with ocular surface optimization with a dietary supplement of omega-3 fatty-acids and preservative-free lubricants are crucial along with patient education to avoid eye rubbing [63,64].

Surgery of keratoconus & ectasia diseases

Until the mid-1990s, corneal transplant was the only available surgical option for visual rehabilitation for keratoconus cases. Currently, there are other procedures, which are less invasive and provide as an alternative to keratoplasty (Table 1). There are basically two indications for surgery in cases of keratoconus and ectasia diseases (Table 2). Surgery is classically indicated when visual acuity is not satisfactory with glasses or contact lenses [56]. However, the advent of crosslinking determines a new horizon to prevent disease progression. The indication of crosslinking is related to the progression of the disease [65]. This procedure is a minimally invasive surgical technique, which combines riboflavin (vitamin B2) and UV type-A (UV-A) to induce crosslinks between the collagen fibrils in the corneal stroma. Riboflavin soaking can be performed after epithelial debridement (Epi-off technique) [65–67]. Alternatively, this procedure can also be done in a transepithelial way (Epi-on technique), with a different type of riboflavin [68]. Clinical studies reported that crosslinking declines the progression of the disease, with a reduction in maximal keratometry readings and improvement of the BCVA [66,67,69]. An age higher than 35 years old, a preoperative corrected distance visual acuity greater than 20/25 and high preoperative keratometry readings were identified as significant risk factors for complications and failure of this treatment [70].

The advent of femtosecond laser revolutionized anterior segment surgery [71]. For example, the dissection technique for implantation of ICRS may be performed manually. However, when it is femtosecond laser-assisted has a more predictable and safer (lower complication rates) results [57,72,73]. The aim of this procedure is to regularize the ectatic cornea, providing high-order aberration magnitude reduction [74,75]. During the last years, this surgical procedure underwent some improvements of the material and implantation nomograms [57]. The Athens Protocol is another surgical option to regularize the cornea and to stop the progression of the disease. With this procedure, we perform a topography-guided PRK (topo-guided PRK) combined with crosslinking [76,77]. The ablation pattern is tissue-sparing and is customized to the irregularity of the front surface of the cornea. Clinical studies have demonstrated visual acuity and quality improvement derived from the corneal surface regularization, without progression of the ectatic process [76,77].

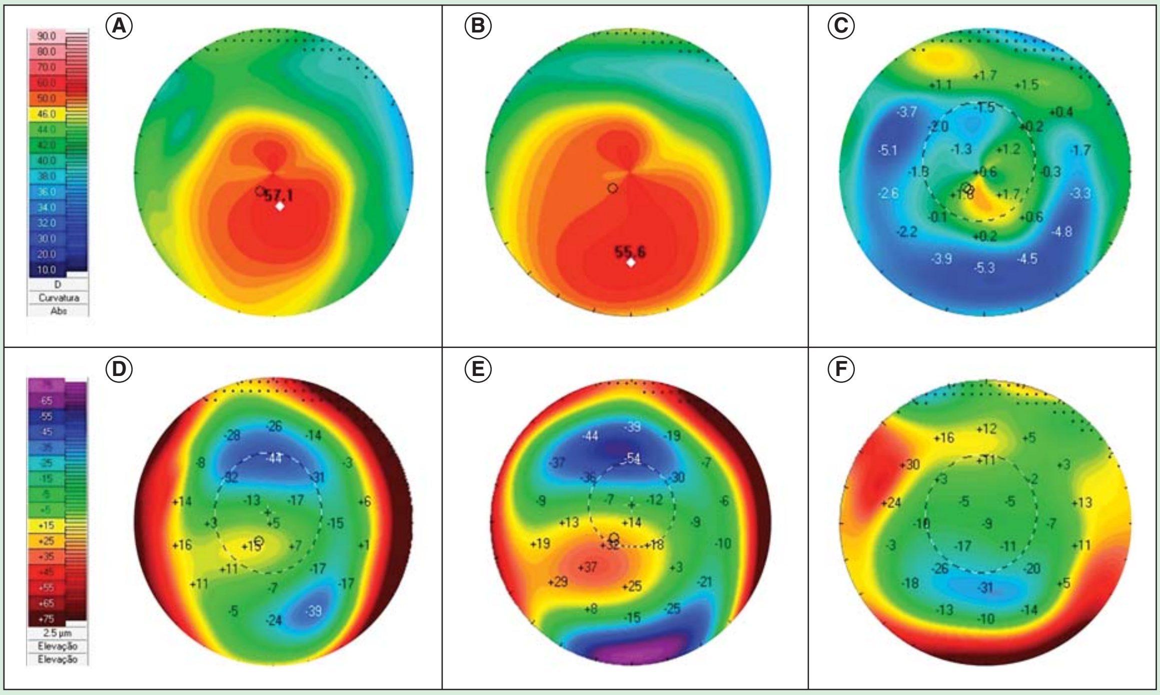

Figure 8. Differential axial curvature (upper row) and anterior elevation (lower row) maps showing flattening and reduction of the corneal irregularity. (A) and **(D)** 12 month after intracorneal ring segment implantation; **(B)** and **(E)** preoperative; **(C)** and **(F)** differential (same reference sphere used in the elevation maps).

Figure 3 shows a decision tree that guides the clinical decision making in keratoconus cases, based on the most important features of the clinical presentation: age at onset, visual acuity, stability and stage (severity) of the disease. Examples 2 to 5 illustrate different medical and surgical approaches for keratoconus cases.

Example 2: Male, 14 years old, presented with progressive visual loss due to keratoconus, more advanced in the left eye (progressed to acute hydrops). Transepithelial crosslinking was performed in the right eye. One year after the procedure (Figure 4), there was improvement of the uncorrected visual acuity (uncorrected visual acuity [UCVA]; 20/100 to 20/40) and of the BCVA (20/25 with −0.50 = −0.75 × 60°).

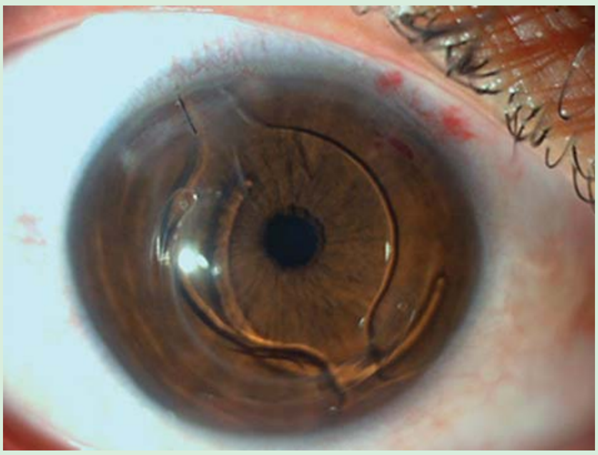

Figure 9. Video image from the immediate postoperative period after implantation of phakic intraocular lens in Therapeutic Bioptics approach.

Example 3: Female, 39 years old, presented with vision loss in the left eye due to asymmetric keratoconus progression and anisometropia (Figure 5). Submitted to Athens Protocol in the left eye, consisting of customized therapeutic laser (phototherapeutic keratectomy–PRK) followed by crosslinking. Clinical improvement was noticed postoperatively: UCVA of 20/100 to 20/60 and BCVA of 20/30 (+0.25 = −4.00 × 108°) to 20/25 (−0.25 = −1.00 × 180°). Refractive error was stable from 6 to 30 months of follow-up. The corneal irregularity reduction, along with the flattening effect, can be observed on the differential map. There was improvement of the K_{max} value (point of maximum curvature; 49.7D to 45.0D) and the anterior astigmatism and elevation magnitudes (+28 microns to +2 microns, respectively) (Figure 6).

Example 4: Female, 40 years old, with prior indication for keratoplasty due to advanced keratoconus with contact lens intolerance (Figure 7). An ICRS implantation was performed in the right eye. At the third month postop, there was improvement of the UCVA (counting fingers at 1 m to 20/160) and of the BCVA (20/200 with −6.00 = −4.00 × 40° to 20/25 with −5.25). Clinical improvement is observed by way of decrease in corneal irregularity on the differential map (Figure 8). Phakic

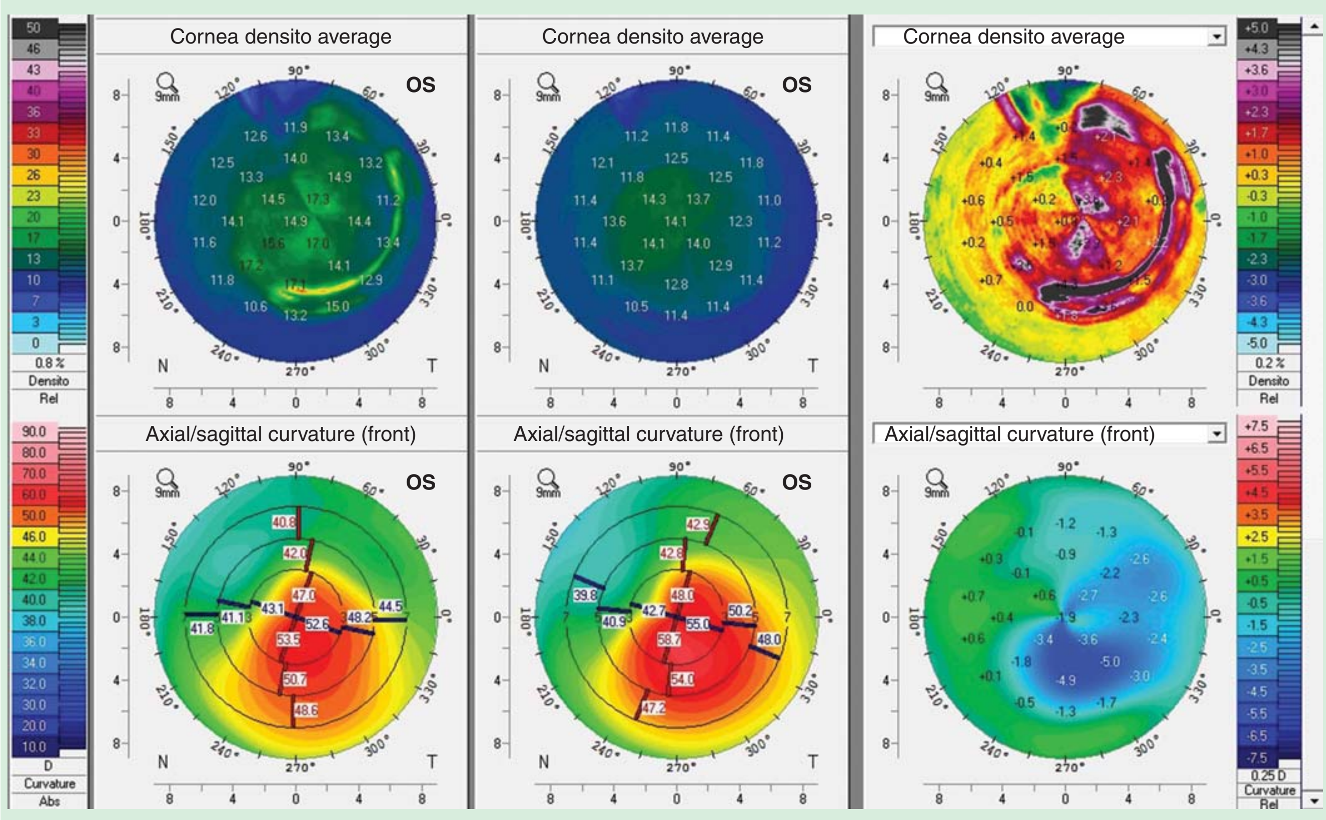

Figure 10. Postoperative, preoperative (6 weeks after femtosecond-assisted intracorneal ring segment and transepithelial crosslinking) and subtraction maps of the average optical density and axial curvature maps.

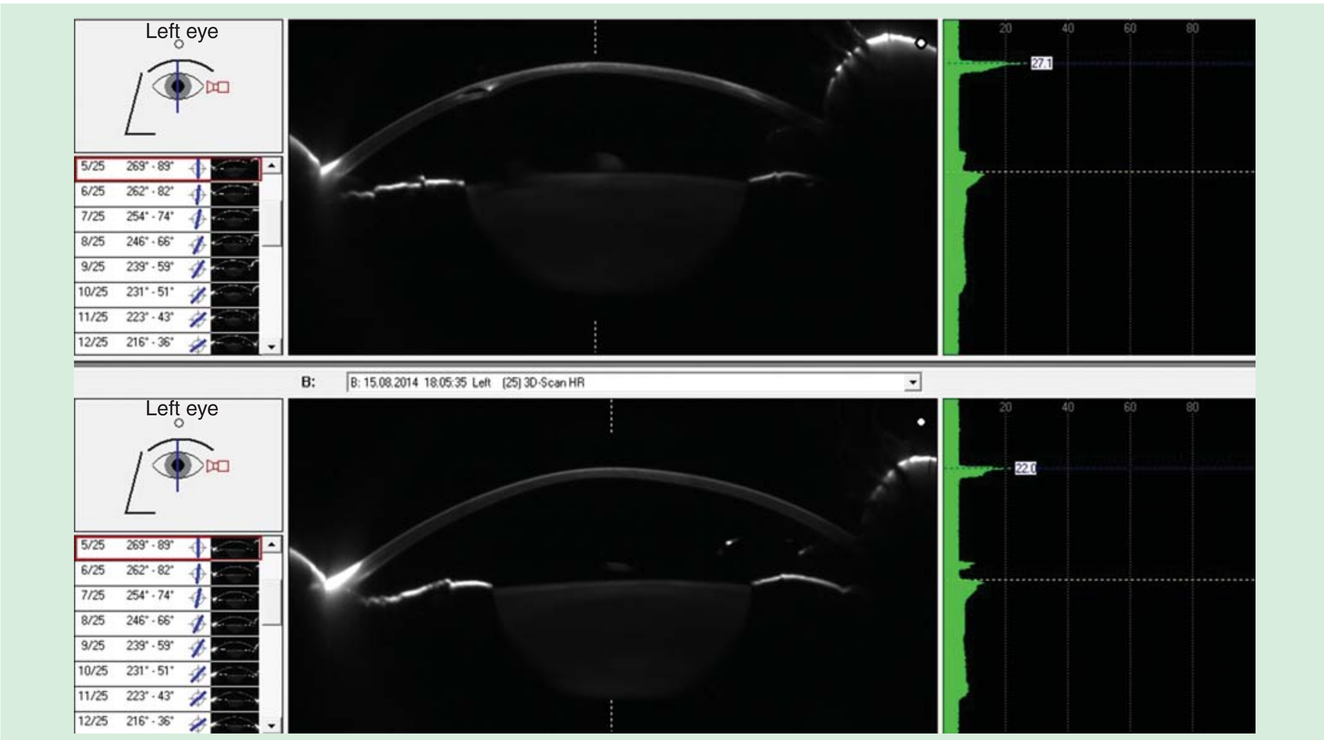

Figure 11. Postoperative and preoperative Scheimpflug imaging on the vertical section.

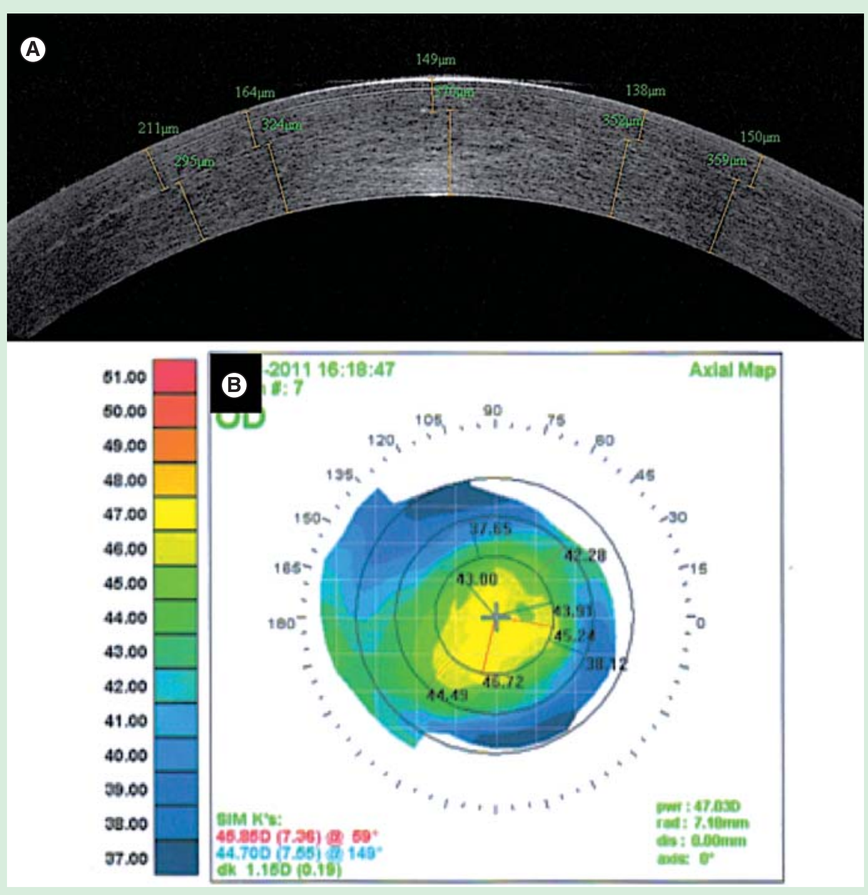

Figure 12. Clinical case with a thick flap without corneal ectasia. (A) Corneal optical coherence tomography and **(B)** anterior sagittal map.

intraocular lens (AcrySof Cachet; Alcon, Fort Worth, Texas) implantation was performed 4 months after the first procedure (FIGURE 9). There was improvement of the UCVA (20/160 to 20/50). The BCVA remained at 20/25 with manifest refraction of $-0.25 = -1.00 \times 17°$ at the 24 month of follow-up.

Example 5: Male, 24 years old, with progressive keratoconus in the left eye and anisometropia. UCVA was 20/20–1 in the right eye and 20/200 in the left eye. Wavefront-assisted manifest refraction was $-0.75 = -5.25 \times 175°$, giving 20/30–2 in the left eye. Femtosecond laser-assisted (FS-200, Alcon, Fort Worth) ICRS implantation was performed, using Keraring (Mediphacos, Belo Horizonte, Brazil) SI6 150[o]with 250 m thickness. ICRS implantation was combined with transepithelial (EpiON) crosslinking. Riboflavin 0.22% solution (VibeX Xtra; Avedro Inc., Waltham, MS, USA) was used. The patient was subjected to 8 min of pulsed UV-A light (1 sec on/1 sec off) at 30 mW/cm^2 (energy dose of 7.2 J/cm^2) with the Avedro KXL. After 6 weeks, the UCVA was 20/30 and the BCVA was 20/25+ (plano = $-1{,}00 \times 170$). FIGURE 10 shows the postoperative corneal flattening, along with the increase of the corneal density (optical scattering). FIGURE 11 demonstrates the ICRS position and demarcation line on the Scheimpflug image.

Clinical & surgical management of post-LASIK ectasia

Post-LASIK ectasia occurs due to an imbalance of the preoperative corneal strength and the structural impact of the surgery. Understanding of the clinical status prior to surgery is crucial, as well as the information regarding the procedure performed. Topography, pachymetry, refractive error and visual acuity are the most relevant preoperative data. In addition to the data related to the procedure (flap thickness, type of cut and maximum depth of photoablation), it is essential to evaluate the geometry and thickness of the flap for a better understanding of the biomechanical impact induced by the surgery. Whenever possible, the stability and progression of the ectasia should be checked [6,10,17,78,79].

For diagnostic purpose, the review of the preoperative ancillary tests (corneal topography and tomography) is relevant. This also allows us to plan the best treatment approach for each patient. Understanding the visual potential of each case is important to exclude amblyopia. Examination of potential visual acuity is quite effective in this regard [79].

As mentioned before, surgery should be considered in order to avoid progression of the disease and to provide a fast visual rehabilitation (TABLE 1) [56,79]. The same surgical approaches for keratoconus may also be indicated in cases of ectasia after LVC. However, there is big difference, because these patients have a greater interest and demand, since they previously performed surgery with the goal of vision correction and independence of optical correction.

Overall, cases with very thick flap have a lesser chance of success with ICRS implantation because there is no tissue support [57]. Athens Protocol is a more suitable option for these cases (Example 6). The results of this procedure show corneal surface regularization combined with marked myopic regression [80]. After checking the stability of these findings, phakic intraocular lens indication also appears valid option (Example 7) [56].

Example 6: Male, 52 years old, with stable LASIK in the right eye (FIGURE 12) and post-LASIK ectasia in the left eye (FIGURE 13) due to an abnormal thick flap. Considering the progressive visual loss in the left eye, the patient was submitted to Athens Protocol.

Example 7: Male, 25 years old, presented with progressive and severe visual loss (UCVA of 1 m counting fingers in both eyes) due to ectasia (FIGURE 14) after bilateral LASIK performed in

2006. The BCVA was 20/30 (−15.0 = −2.50 × 15°) in the right eye and 20/80 (−14.25 = −6.0 × 0°) in the left eye. The thinnest pachymetry value was 408 microns in the right eye and 395 microns in the left eye. Given the severity of the clinical picture, the moderately thin cornea and the presence of contact lens intolerance, it was decided to perform transepithelial crosslinking in both eyes as an alternative to keratoplasty. After refractive stabilization (with two similar measures within a 1-month interval), phakic intraocular lens implantation was performed (AcrySof Cachet) in both eyes. The UCVA improved to 20/30 in the right eye and 20/25 in the left eye at the 24-month follow-up (Figure 15).

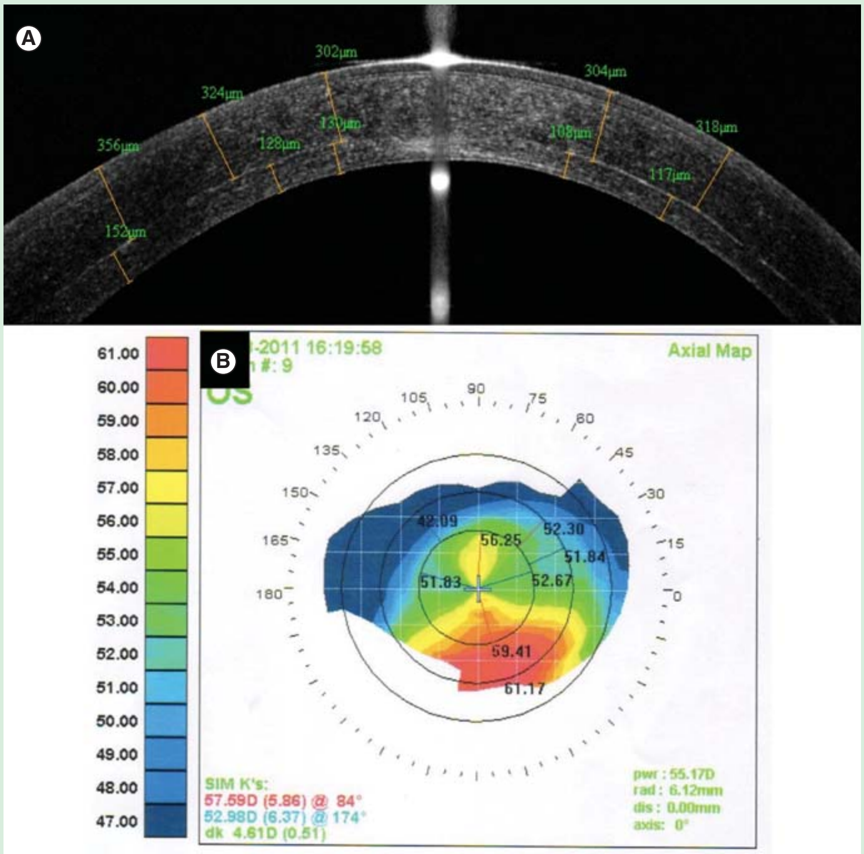

Figure 13. Clinical case with post-LASIK ectasia due to a thick corneal flap. **(A)** Corneal optical coherence tomography and **(B)** anterior sagittal map.

Expert commentary

In 2012, it was proposed that keratoconus and ectatic corneal diseases represent a new subspecialty in ophthalmology. The advances in complementary investigation and therapeutic procedures enable less invasive alternatives, which markedly reduces the need for transplantation in these patients [57,81,82].

Ancillary exams play a major role in the diagnosis of this disease. Advanced clinical analysis should be performed in every patient with confirmed diagnosis and even those in whom it is suspected. For this purpose, detailed clinical history and ophthalmological exam should be obtained, along with corneal topography, tomography and biomechanics assessment [4,6]. Other exams, such as wavefront analysis and ocular biometry, are important to understand the patient's visual complaints. We found that wavefront analysis was also relevant in facilitating the refraction in these patients, showing best-corrected distance visual acuity improvement in cases with some degree of contact lens intolerance [61].

Once the diagnosis of keratoconus is accomplished, patient education is fundamental. In the very early stages of the disease, spectacle lenses are an option, especially for patients who achieve 20/40 or better. In some patients, spectacles do not correct the irregular astigmatism and rigid contact lenses may provide better correction. Contact lenses represent the treatment of choice in nearly 90% of patients with keratoconus, with the selection of type of lens dependent on the stage of the disease [61,62].

Discussion of surgical options is the end-point for patients who cannot achieve good vision with spectacles or have contact lens intolerance. Therapeutic bioptics is also an interesting concept that allows faster visual rehabilitation, by combining procedures of therapeutic and refractive purposes [55,56].

Despite the lack of large, multicenter, prospective randomized trials, crosslinking has gradually become a first line of treatment for keratoconus and other ectatic conditions [65,82]. Previous studies demonstrated that this surgical option increases the rigidity and stiffness of the cornea, halting the progression of the ectasia disorder. Its effects are noticed on corneal topography and pachymetry, but we need to wait at least 4–6 months. The improvement of the corneal regularity is also associated with the BCVA increase, especially because of the irregular astigmatism decrease and the topographic reshaping process. Stability of these outcomes was documented several years after the procedure [66,67,83]. Regarding corneal pachymetry, there is a temporary thinning of the central corneal thickness by 30–50 microns. This can be explained by the epithelium removal at the beginning of the procedure and by the dehydration induced by the exposure to UV light. The effect in the corneal biomechanical behavior can be assessed with the CorVis ST, featuring less deformation response [44,46]. Few complications have been described. A mild and transient stromal edema with hazy appearance is common, but usually solves after 4 weeks. Other reported complications are delayed re-epithelization, sterile infiltrates, corneal ulceration, scarring and even

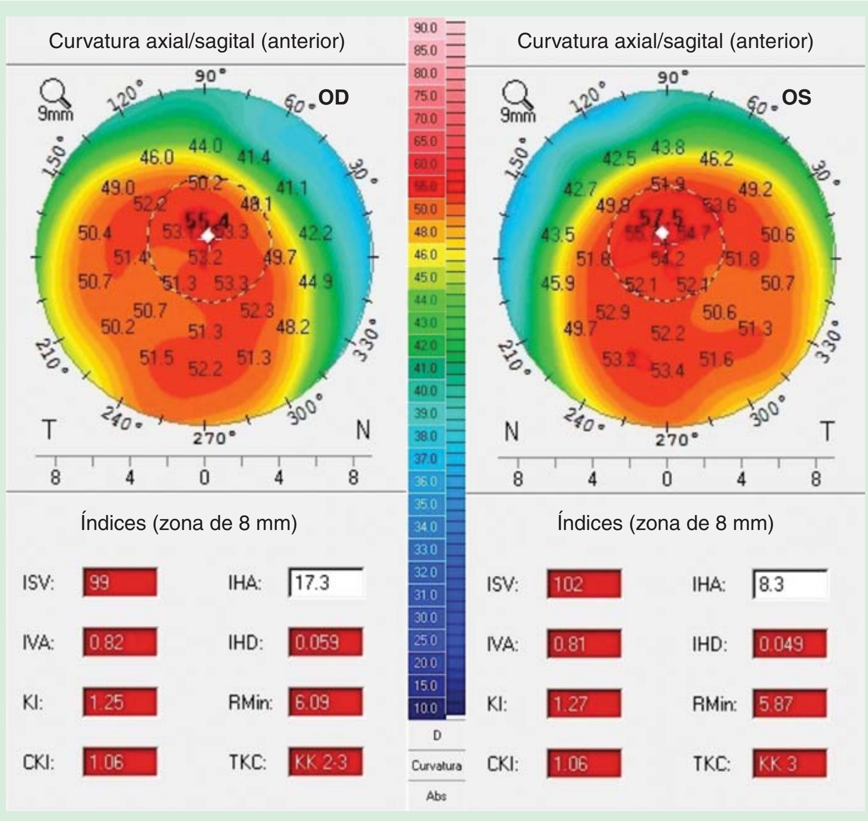

Figure 14. Preoperative axial curvature map of ectasia after LASIK in both eyes. BCVA was 20/30 (–15.0 = –2.50 × 15°) in OD and 20/80 (–14.25 = –6.00 × 0°) in OS. OD: Right eye; OS: Left eye.

progression of the ectasia [70]. One of the improvements in crosslinking treatment protocols is the Epi-on modalidade that does not require epithelial removal [68]. This has the advantage of preventing the risk of infection and stromal scarring, and also contributes to enhance the patient comfort.

ICRS and Athens Protocol are effective methods to improve visual quality and contact lens tolerance. The ICRS implantation technique should be assisted with femtosecond laser. With this technology, the tunnel's depth is more precise and is associated with a lower complication rate [72]. Since the introduction of crosslinking, the excimer laser became a useful tool for the ectasia management. In our algorithm, we also consider the Athens Protocol [76]. This option is more suitable in patients who have sufficient pachymetry after the ablation to allow the crosslinking treatment (i.e., superior to 400 microns). Another important decision point is the point of maximum curvature (K_{max}) of the cornea. If the K_{max} is superior to 52 D, we may consider other treatment modalities, such as ICRS.

A sequential procedure, such as phakic intraocular lens implantation or cataract extraction, is an option for the treatment of residual low-order aberrations. This approach should only be performed after regularizing the corneal structure and should be weighted according to each case [56,75].

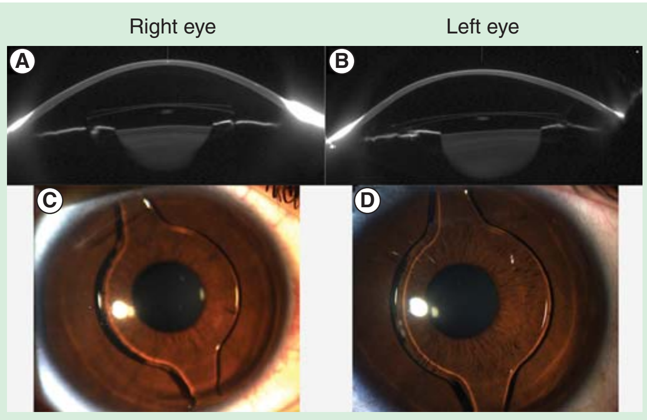

Figure 15. Clinical case with post-LASIK ectasia treated submitted to transepithelial crosslinking followed by phakic intraocular lens implantation in both eyes. (A) and **(B)** Scheimpflug image after transepithelial crosslinking of the right and left eyes, respectively; **(C)** and **(D)** Slit-lamp photograph showing phakic intraocular lens implant in the right and left eyes, respectively.

Five-year view

Compared to topography, CT has proven to be more effective in enhancing accuracy and specificity for diagnosing corneal ectatic diseases. Additional ancillary tests, such as high-resolution optical coherence tomography and very-high-frequency ultrasound, will provide a more detailed characterization of corneal architecture, along with corneal biomechanics evaluation [12,32,84]. Fancy diagnostic approaches will also include new genetic testing tools.

The future management of corneal ectatic disorders will hold on the 'Therapeutic Bioptics' concept, incorporating multiple treatment modalities, both simultaneous and/or sequential. In terms of corneal reshaping, newer ICRS implantation nomograms and techniques will provide better results, as well as improved topo-guided ablations profiles [56]. With the advent of corneal crosslinking, the spectrum of keratoconus management now includes the prevention and the treatment of progression of disease. It is anticipated that newer riboflavin soaking techniques and UV-irradiation protocols will allow a more customized procedure to each patient. Considering the risk of progression of keratoconus and the need for keratoplasty at advanced stages of the disease, crosslinking will probably be considered in any patient diagnosed with progressive, forme fruste or clinically significant keratoconus.

Other innovations in the keratoplasty field may also emerge. In 2013, Melles and coworkers presented the isolated Bowman layer transplantation procedure. They claim that this option may be safe and effective in eyes with progressive and advanced keratoconus. The procedure may be performed to postpone penetrating or deep anterior lamellar keratoplasty [85].

Financial & competing interests disclosure

R Ambrósio has been a consultant for Oculus (Wetzlar, Germany). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The advent of refractive surgery enabled the greatest advances in the understanding of pathophysiology, diagnosis and treatment of ectatic diseases. The different associations that highlight this importance varies from the need of early diagnosis in the screening process of selecting candidates for laser vision correction to the impact of new technologies related to refractive surgery in the treatment of these diseases.
- Corneal ectasia is a condition characterized by biomechanical structural failure, which leads to thinning and tissue protrusion without a clear and an acute inflammatory process.
- Keratoconus is the most common ectatic disorder and is identified in about 1–5% of candidates for refractive surgery. Other disorders that are classified within this group of natural ectatic diseases are pellucid marginal degeneration and keratoglobus.
- Ectasia progression can also occur after trauma or procedures associated with tissue loss, such as radial keratotomy, LASIK and PRK. The proper selection of candidates for refractive surgery is the key to prevent this severe complication.
- Compared to topography, corneal tomography provides a 3D image of the cornea, allowing a more accurate diagnosis of very early forms of ectasia. Other ancillary exams are essential to pathophysiological understanding, patient education and treatment planning.
- Management of ectatic disorders includes control of allergy and ocular surface optimization, since eye rubbing is directly related to disease progression. For visual rehabilitation, the glasses and contact lenses are the first option available.
- The two indications for surgery in cases of keratoconus and ectasia diseases are unsatisfactory visual acuity with glasses or contact lenses and disease progression.
- Crosslinking is specially indicated in cases with progressive keratoconus. This procedure stabilizes the ectatic process, along with topographic and visual improvement.
- Currently, therapeutic procedures are presented as a less invasive alternative to keratoplasty for visual rehabilitation. The main goal is to provide a state that vision is possible to be corrected with sphere-cylindrical refraction.
- Intracorneal ring segment and Athens Protocol are valuable approaches to reduce the irregularity induced by the ectatic disease, in order to provide visual improvement. These procedures may also be combined in various ways according to the need and indication in each case.
- In post-LASIK ectasia patients, surgery should also be considered in order to avoid progression of the disease and to provide a fast visual rehabilitation. It is essential to review the preoperative data, in order to understand the pathophysiological mechanism.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol 1984;28(4):293-322
2. Belin MW, Asota IM, Ambrosio R Jr, Khachikian SS. What's in a name: keratoconus, pellucid marginal degeneration, and related thinning disorders. Am J Ophthalmol 2011;152(2): 157-162 e151
3. Ambrosio R Jr, Klyce SD, Wilson SE. Corneal topographic and pachymetric screening of keratorefractive patients. J Refract Surg 2003;19(1):24-9
   •• **This paper reviews the incidence of corneal abnormalities detected in the preoperative examination, using videokeratography and pachymetry that excluded patients with LASIK or photorefractive keratectomy; corneal topography and pachymetry are indispensable tools in the preoperative screening of refractive surgery candidates.**
4. Ambrosio R Jr, Nogueira LP, Caldas DL, et al. Evaluation of corneal shape and biomechanics before LASIK. Int Ophthalmol Clin 2011;51(2):11-38
   • **This paper reviews the incidence of corneal abnormalities detected in the preoperative examination, using videokeratography and pachymetry that excluded patients for LASIK or photorefractive keratectomy; corneal topography and pachymetry are indispensable tools in the preoperative screening of refractive surgery candidates.**
5. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. J Refract Surg 1998;14(3):312-17
6. Ambrosio R Jr, Dawson DG, Salomao M, et al. Corneal ectasia after LASIK despite low preoperative risk: tomographic and biomechanical findings in the unoperated,

stable, fellow eye. J Refract Surg 2010; 26(11):906-11

- **This paper reports a case of progressive corneal ectasia after LASIK with no detectable preoperative risk factors; it also presents the 3D corneal tomographic and biomechanical findings on the contralateral unoperated eye that would be considered low risk for ectasia and thereby a good LASIK candidate based on the Ectasia Risk Score System.**

7. Koch DD. Refractive surgery for keratoconus: a new approach. J Cataract Refract Surg 2000;26(8):1099-100
8. Ambrosio R Jr, Ramos I, Faria-Correia F, Belin MW. Tomographic Screening for Ectasia Susceptibility - Analysis must go beyond corneal curvature and central thickness. Cataract Refract Surg Today Europe 2012;20-5
9. Ramos IC, Correa R, Guerra FP, et al. Variability of subjective classifications of corneal topography maps from LASIK candidates. J Refract Surg 2013;29(11): 770-5
10. Ambrosio R Jr, Randleman JB. Screening for ectasia risk: what are we screening for and how should we screen for it? J Refract Surg 2013;29(4):230-2
11. Ambrósio R Jr, Ramos I, Lopes B, et al. Assessing ectasia susceptibility prior to LASIK: the role of age and residual stromal bed (RSB) in conjunction to Belin-Ambrósio deviation index (BAD-D). Rev Bras Oftalmol 2014;73:75-80
12. Roberts CJ, Dupps WJ Jr. Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg 2014; 40(6):991-8
13. McMonnies CW. Abnormal rubbing and keratectasia. Eye Contact Lens 2007; 33(6 Pt 1):265-71
14. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998;42(4):297-319
15. Krachmer JH. Pellucid marginal corneal degeneration. Arch Ophthalmol 1978;96(7): 1217-21
16. Belin MW, Ambrosio R. Scheimpflug imaging for keratoconus and ectatic disease. Indian J Ophthalmol 2013;61(8):401-6
17. Dawson DG, Randleman JB, Grossniklaus HE, et al. Corneal ectasia after excimer laser keratorefractive surgery: histopathology, ultrastructure, and pathophysiology. Ophthalmology 2008; 115(12):2181-91.e2181
18. Randleman JB, Russell B, Ward MA, et al. Risk factors and prognosis for corneal ectasia after LASIK. Ophthalmology 2003; 110(2):267-75
19. Randleman JB, Caster AI, Banning CS, Stulting RD. Corneal ectasia after photorefractive keratectomy. J Cataract Refract Surg 2006;32(8):1395-8
20. Amsler M. The forme fruste of keratoconus. Wien Klin Wochenschr 1961;73:842-3
21. Klyce SD. Computer-assisted corneal topography. High-resolution graphic presentation and analysis of keratoscopy. Invest Ophthalmol Vis Sci 1984;25(12): 1426-35
22. Maeda N, Klyce SD, Tano Y. Detection and classification of mild irregular astigmatism in patients with good visual acuity. Surv Ophthalmol 1998;43(1):53-8
23. Lee BW, Jurkunas UV, Harissi-Dagher M, et al. Ectatic disorders associated with a claw-shaped pattern on corneal topography. Am J Ophthalmol 2007;144(1):154-6
24. Maeda N, Klyce SD, Smolek MK. Comparison of methods for detecting keratoconus using videokeratography. Arch Ophthalmol 1995;113(7):870-4
25. Rabinowitz YS, Rasheed K, Yang H, Elashoff J. Accuracy of ultrasonic pachymetry and videokeratography in detecting keratoconus. J Cataract Refract Surg 1998;24(2):196-201
26. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. J Cataract Refract Surg 1999;25(10):1327-35
27. Ambrosio R Jr, Belin MW. Imaging of the cornea: topography vs tomography. J Refract Surg 2010;26(11):847-9

- **This paper highlights the difference between CT and topography concepts; it also focuses on the advantages of CT in refractive surgery screening.**

28. Ambrosio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. J Cataract Refract Surg 2006;32(11):1851-9

- •• **This paper shows the importance of corneal-thickness spatial profile and corneal-volume distribution to differentiate keratoconic corneas from normal corneas; these tomographic parameters were different between keratoconic and normal corneas and can also serve as indices to diagnose keratoconus and screen refractive candidates.**

29. Ambrosio R Jr, Caiado AL, Guerra FP, et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract Surg 2011;27(10): 753-8
30. Reinstein DZ, Gobbe M, Archer TJ, et al. Epithelial, stromal, and total corneal thickness in keratoconus: three-dimensional display with artemis very-high frequency digital ultrasound. J Refract Surg 2010; 26(4):259-71
31. Li Y, Tan O, Brass R, et al. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. Ophthalmology 2012;119(12):2425-33
32. Reinstein DZ, Archer TJ, Gobbe M. Corneal epithelial thickness profile in the diagnosis of keratoconus. J Refract Surg 2009;25(7):604-10
33. Faria-Correia F, Ramos IC, Lopes B, et al. Topometric and Topographic Indices for the Diagnosis of Keratoconus. Int J Kerat Ect Cor Dis 2012;1(2):92-9
34. Ambrosio R Jr, Valbon BF, Faria-Correia F, et al. Scheimpflug imaging for laser refractive surgery. Curr Opin Ophthalmol 2013;24(4):310-20
35. Klyce SD. Chasing the suspect: keratoconus. Br J Ophthalmol 2009;93(7):845-7
36. Randleman JB, Trattler WB, Stulting RD. Validation of the Ectasia Risk Score System for preoperative laser in situ keratomileusis screening. Am J Ophthalmol 2008;145(5): 813-18

- •• **This paper analyzes the epidemiologic features of ectasia after excimer laser corneal refractive surgery, in order to identify risk factors for its development; a quantitative screening strategy can be used to identify eyes at risk for developing ectasia after LASIK.**

37. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 2008;115(1):37-50

- •• **This paper validates the Ectasia Risk Score System for identifying patients at high risk for developing ectasia after LASIK; this screening methodology represents a significant improvement over previously utilized screening strategies.**

38. Klein SR, Epstein RJ, Randleman JB, Stulting RD. Corneal ectasia after laser in situ keratomileusis in patients without apparent preoperative risk factors. Cornea 2006;25(4):388-403

39. Chan CC, Hodge C, Sutton G. External analysis of the Randleman Ectasia Risk Factor Score System: a review of 36 cases of post LASIK ectasia. Clin Experiment Ophthalmol 2010;38(4):335-40
40. Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in eyes with normal topography. J Refract Surg 2010;26(4): 241-50
41. Ambrosio R Jr, Wilson SE. Complications of laser in situ keratomileusis: etiology, prevention, and treatment. J Refract Surg 2001;17(3):350-79

•• **This paper highlights the importance of careful preoperative screening in order to prevent potential complications of LASIK; timely treatment of postoperative complications is critical to an optimal outcome; most complications can be treated effectively and have minimal effect on the final outcome after surgery, if appropriate methods are used for management.**

42. Ambrosio R Jr, Luz A, Lopes B, et al. Enhanced ectasia screening: the need for advanced and objective data. J Refract Surg 2014;30(3):151-2
43. Roberts C. The cornea is not a piece of plastic. J Refract Surg 2000;16(4):407-13
44. Ambrosio R Jr, Ramos I, Luz A, et al. Dynamic ultra-high speed scheimpflug imaging for assessing corneal biomechanical properties. Rev Bras Oftalmol 2013;72
45. Faria-Correia F, Ramos I, Valbon B, et al. Scheimpflug-based tomography and biomechanical assessment in pressure-induced stromal keratopathy. J Refract Surg 2013;29(5):356-8
46. Correia FF, Ramos I, Roberts CJ, et al. Impact of chamber pressure and material properties on the deformation response of corneal models measured by dynamic ultra-high-speed Scheimpflug imaging. Arq Bras Oftalmol 2013;76(5):278-81
47. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg 2005;31(1):156-62
48. Fontes BM, Ambrosio R Jr, Jardim D, et al. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. Ophthalmology 2010;117(4):673-9
49. Wang Y, Rabinowitz YS, Rotter JI, Yang H. Genetic epidemiological study of keratoconus: evidence for major gene determination. Am J Med Genet 2000; 93(5):403-9
50. Jafri B, Li X, Yang H, Rabinowitz YS. Higher order wavefront aberrations and topography in early and suspected keratoconus. J Refract Surg 2007;23(8): 774-81
51. Sibug ME, Datiles MB 3rd, Kashima K, et al. Specular microscopy studies on the corneal endothelium after cessation of contact lens wear. Cornea 1991;10(5): 395-401
52. Ernst BJ, Hsu HY. Keratoconus association with axial myopia: a prospective biometric study. Eye Contact Lens 2011;37(1):2-5
53. Ozgurhan EB, Kara N, Yildirim A, et al. Evaluation of corneal microstructure in keratoconus: a confocal microscopy study. Am J Ophthalmol 2013;156(5):885-93.e882
54. Ambrósio Jr. R. Cirurgia refrativa terapêutica: por que diferenciar? Rev Bras Oftalmol 2013;72:85-6
55. Ambrosio R Jr. Cirurgia refrativa terapêutica: por que diferenciar? Rev Bras Oftalmol 2013;72:85-6
56. Ambrosio R Jr. Intracorneal ring segment, phakic IOL implantation enable keratoconus management without keratoplasty. Ocular Surgery News US Edition. 2011;12
57. Pinero DP, Alio JL. Intracorneal ring segments in ectatic corneal disease - a review. Clin Experiment Ophthalmol 2010; 38(2):154-67
58. Cochener B, Savary-LeFloch G, Colin J. Effect of intrastromal corneal ring segment shift on clinical outcome: one year results for low myopia. J Cataract Refract Surg 2000;26(7):978-86
59. Rush SW, Han DY, Rush RB. Optical coherence tomography-guided transepithelial phototherapeutic keratectomy for the treatment of anterior corneal scarring. Am J Ophthalmol 2013;156(6):1088-94
60. Kelly TL, Coster DJ, Williams KA. Repeat penetrating corneal transplantation in patients with keratoconus. Ophthalmology 2011;118(8):1538-42
61. Ambrosio R Jr, Caldas DL, Silva RS, et al. Impacto da análise do wavefront na refractometria de pacientes com ceratocone. Rev Bras Oftalmol 2010;29:294-300
62. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. Cornea 2011;30(12):1510-16
63. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. Ophthalmology 2007;114(1):76-9
64. Olenik A. Effectiveness and tolerability of dietary supplementation with a combination of omega-3 polyunsaturated fatty acids and antioxidants in the treatment of dry eye symptoms: results of a prospective study. Clin Ophthalmol 2014;8:169-76
65. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135(5):620-7
66. Vinciguerra P, Albe E, Trazza S, et al. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. Ophthalmology 2009;116(3):369-78
67. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol 2010;149(4): 585-93
68. Mastropasqua L, Nubile M, Calienno R, et al. Corneal cross-linking: intrastromal riboflavin concentration in iontophoresis-assisted imbibition versus traditional and transepithelial techniques. Am J Ophthalmol 2014;157(3):623-30.e621
69. Koller T, Iseli HP, Hafezi F, et al. Scheimpflug imaging of corneas after collagen cross-linking. Cornea 2009;28(5): 510-15
70. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009; 35(8):1358-62
71. Ambrosio R Jr. A revolução dos lasers de femtossegundo na oftalmologia. Rev Bras Oftalmol 2011;70(4):207-10
72. Pinero DP, Alio JL, El Kady B, et al. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. Ophthalmology 2009;116(9): 1675-87
73. Coskunseven E, Kymionis GD, Tsiklis NS, et al. Complications of intrastromal corneal ring segment implantation using a femtosecond laser for channel creation: a survey of 850 eyes with keratoconus. Acta Ophthalmol 2011;89(1):54-7
74. Alfonso JF, Fernandez-Vega Cueto L, Baamonde B, et al. Inferior intrastromal corneal ring segments in paracentral keratoconus with no coincident topographic and coma axis. J Refract Surg 2013;29(4): 266-72
75. Alfonso JF, Fernandez-Vega L, Lisa C, et al. Collagen copolymer toric posterior chamber phakic intraocular lens in eyes with

keratoconus. J Cataract Refract Surg 2010; 36(6):906-16

76. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg 2009;25(9):S812-18

77. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. Cornea 2007;26(7):891-5

78. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract Surg 2007;33(9):1530-8

79. Ambrosio R Jr, Jardim D, Netto MV, Wilson SE. Management of unsuccessful LASIK surgery. Compr Ophthalmol Update 2007;8(3):125-41.discussion 143-124

80. Kanellopoulos AJ, Binder PS. Management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK and collagen cross-linking: the athens protocol. J Refract Surg 2011;27(5):323-31

81. Gosavi VV, Hardten DR. Developments in diagnostic tools for corneal ectasia. Expert Rev Ophthalmol 2010;5(4):475-81

82. Vanathi M, Bypareddy R. A. P. Cornea collagen crosslinking using UVA light and riboflavin for keratoconus. Expert Rev Ophthalmol 2012;7(1):33-44

83. Vinciguerra P, Camesasca FI, Albe E, Trazza S. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. J Refract Surg 2010;26(7): 486-97

84. Touboul D, Gennisson JL, Nguyen TM, et al. Supersonic shear wave elastography for the in vivo evaluation of transepithelial corneal collagen cross-linking. Invest Ophthalmol Vis Sci 2014;55(3):1976-84

85. van Dijk K, Parker J, Tong CM, et al. Midstromal isolated Bowman layer graft for reduction of advanced keratoconus: a technique to postpone penetrating or deep anterior lamellar keratoplasty. JAMA Ophthalmol 2014;132(4):495-501